Amendments to the Drawings:

Please replace Figs. 4 and 9 with the attached new Figs. 4 and 9, which are correctly labeled as Fig. 4A, Fig. 4B, Fig. 9A, and Fig. 9B.

REMARKS/ARGUMENTS

Claims 1-3, 10-19, 25-26, and 29-35 are pending in this application. Claims 1, 26, and 33 are amended to more clearly define the invention by clarifying that the multimer formed by the fusion polypeptides of the invention is formed through interactions between multimerizing components. Support for this amendment is found at page 20, lines 4-10. Claims 26 and 33 are further amended to clarify that the dimeric IL-18 antagonist comprises two fusion polypeptides, each having the three specified components. Support for this amendment is found throughout the specification, e.g., page 25, lines 14-17. Claim 11 is amended to delete the phrase "light chain of IgG". No new matter is added by the claim amendments and new claims, and the Examiner is respectfully requested to enter them.

I. Formal Matters

A. The abstract was objected to as from the wrong PCT application (PCT/US99/22253 instead of PCTUS99/22045). Accordingly, the specification is amended to replace the incorrect abstract with a new abstract.

B. The title was held not to be descriptive. Accordingly, the specification is amended above to amend the title as shown.

II. Rejection Under 35 USC § 102(a).

Claims 1-3, 10-19, 25-26, and 29-35 are rejected as anticipated by Sims et al. (WO 99/37772). This rejection is respectfully traversed.

The invention as claimed. Amended claim 1 is drawn to a nucleic acid molecule encoding a fusion polypeptide that forms a multimer capable of binding interleukin-18 (IL-18) to form a nonfunctional complex, comprising (a) a nucleotide sequence encoding a first fusion polypeptide component comprising the amino acid sequence of an IL-18 binding portion of an extracellular domain of a specificity determining component of an IL-18 receptor; (b) a nucleotide sequence encoding a second fusion polypeptide component comprising the amino acid sequence of an IL-18 binding portion of an extracellular domain of a signal transducing component of an IL-18 receptor; and (c) a nucleotide sequence encoding a third fusion polypeptide component comprising the amino acid sequence of a multimerizing component, wherein the multimer is formed due to the interactions between multimerizing components. Claim 10 specifies a multimerizing component that comprises an immunoglobulin derived domain. Claim 11 specifies that the immunoglobulin derived domain is selected from the group consisting of the Fc domain of IgG and the heavy chain of IgG. Claims 13 and 14 are drawn to a composition comprising a multimer or dimer of a fusion polypeptide of the invention.

Claim 26 is drawn to an isolated nucleic acid molecule encoding a fusion polypeptide that forms a dimer capable of binding interleukin-18 (IL-18) to form a nonfunctional complex, comprising a first and second fusion polypeptide, wherein each fusion polypeptide comprises the amino acid sequence of an IL-18 binding portion of an extracellular domain of a specificity determining component of an IL-18 receptor, the amino acid sequence of an IL-18 binding portion of an extracellular domain of a signal transducing component of an IL-18 receptor, and the amino acid sequence of a multimerizing component, wherein the multimer is formed due to the interactions between multimerizing components. Claim 33 is drawn to a dimeric interleukin-18 (IL-18) antagonist capable of binding IL-18 to form a nonfunctional complex, comprising first and second fusion polypeptides, each polypeptide comprising a first component comprising the amino acid sequence of an IL-18 binding portion of an extracellular domain of a specificity determining component of an IL-18 receptor; a second component comprising the amino acid sequence of an IL-18 binding portion of an extracellular domain of a signal transducing component of an IL-18 receptor; and a third component comprising the amino acid sequence of a multimerizing component, wherein the dimer is formed due to the interactions between multimerizing components.

The cited WO 99/3772 prior art reference. Sims et al. describes multimeric IL-18 receptor polypeptides consisting of IL-1Rrp and AcPL, or fragments thereof. The polypeptides can be co-expressed as dimers formed from fusion proteins IL-1-Rrp:Fc and AcPL:Fc (page 3, lines 11-14). Alternatively, the IL-18 receptor may comprise fragments of one receptor complexed with fragments of the other receptor (page 4, lines 39-40). The two receptor components may be attached through a covalent or non-covalent linkage, e.g., a peptide linker (page 7, line 34 to page 8, line 12).

The analysis under § 102(a). A *prima facie* case of anticipation requires that a single prior art reference teach all of the elements and limitations of the claimed subject matter. In re Robertson, 169 F.3d 743, 745, 49 U.S.P.Q.2D (BNA) 1949, 1950 (Fed. Cir. 1999). The single reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. Crown Operations International, Ltd. v. Solutia Inc., 289 F.3d 1367, 1375, 62 U.S.P.Q.2D (BNA) 1917, 1921 (Fed. Cir. 2002); In re Spada, 911 F.2d 705, 708, 15 U.S.P.Q.2D (BNA) 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it").

Applicants respectfully submit that a careful reading of the cited prior art reference shows that Sims et al. does not disclose or suggest a single fusion polypeptide having two receptor components connected to a single Fc component.

Analysis of the Examiner's stated support for anticipation.

In making the novelty rejection, the Examiner summarizes the disclosure of Sims et al. as follows (Office action dated 30 Aug 2004, page 5, line 10 to page 6, line 7).

1. Sims et al. teaches heterodimeric receptor complexes that bind IL-18;

2. Sims et al. teach that dimeric IL-18 receptor complexes comprising IL-1Rrp1 and AcPL or fragments thereof may be covalently linked by a polypeptide linker to make fusion proteins;

3. Sims et al. teach that AcPL/IL-1RrP1 dimers can be prepared by fusing one of the receptor subunits to the constant region of an immunoglobulin [heavy] chain and fusing the other receptor to the constant region of an immunoglobulin light chain, and that cells transfected with the DNA encoding these fusion proteins can produce these heterodimers to form multimers;

4. Sims et al. teach that recombinant fusion proteins can be constructed with the C-terminal portion of AcPL fused to the N-terminal portion of IL-1Rrp1, or constructed with the C-terminal portion of IIL-1-Rrp1 fused to the N-terminal portion of AcPL.

Applicants respectfully point out that the Examiner's summary of Sims et al. does not support a *prima facie* case of anticipation. The heterodimeric receptor complexes of Sims et al. are of two types: (i) a fusion heterodimeric protein comprising an antibody light chain polypeptide attached to the C-terminus of a soluble first polypeptide or a soluble second polypeptide, and an antibody heavy chain polypeptide attached to the C-terminus of a soluble first polypeptide or a soluble second polypeptide (claim 8) (see also heterodimeric mIL-1Rrp1-Fc/mAcPL-Fc molecules described in Example 4, page 27, lines 36-37), or (ii) AcPL linked to IL-1Rrp1 (see, for example, page 22, line 40). The latter fusion protein (ii) is nowhere described in the specification as including a multimerizing component.

In contrast to Sims et al, amended claim 1 requires a nucleic acid molecule to encode a fusion polypeptide that forms a multimer capable of binding IL-18, where the fusion polypeptide has two receptor components and a multimerizing component, wherein the multimer is formed due to the interaction between multimerizing components. In other words, claim 1 covers a nucleic acid which encodes a fusion polypeptide that multimerizes with a second fusion polypeptide to produce a multimer that consists of 4 receptor components.

Sims et al. discloses a fusion polypeptide that either has (i) one receptor component and an immunoglobulin domain component, or (ii) two receptor components covalently linked and separated by a peptide linker that functions as a spacer. Embodiment (i) in which each receptor component is on a different fusion protein can form a dimer with each other through the Fc components, but embodiment (ii) having two receptor components on a single fusion protein cannot form a dimer. Thus, although Sims et al describes an Fc component, the Fc component is used to form a dimer between two receptor components, rather than between two fusion proteins each of which contain two receptor components.

A careful reading of Sims et al. reveals that a peptide linker is not equivalent to a multimerizing component. As described at page 7, line 34 to page 8, line 21, a peptide linker is employed to separate the two receptor domains by a sufficient distance to ensure that each domain is able to fold into its proper secondary and tertiary structure. The peptide linkers of Sims et al. are must be placed between the two receptor components and do not function as multimerizing components. In contrast, the instant amended claims specify that the mutimerizing components can be located upstream of, between, or down stream of, the two receptor components (Specification, p.21, lines 11-16) and the interaction among the multimerizing components leads to the formation of multimers.

Accordingly, Applicants submit that Sims et al. does not anticipate amended claim 1 or dependent claims 2, 3, 10-19, and 29-30.

Amended claim 26 differs from claim 1 in that the multimer is limited to a dimer. Therefore, the above arguments are fully applicable to this rejection and applicants submit that the Examiner has failed to establish a *prima facie* case of anticipation against claim 26 and dependent claims 31-32 because the single fusion protein having two receptor components disclosed by Sims et al. is not capable of dimerizing.

Accordingly, Applicants submit that Sims et al. does not anticipate amended claim 26 or dependent claims 31-32.

Amended claim 33 is drawn to a dimeric IL-18 antagonist comprising two fusion polypeptides, each polypeptide having (1) an extracellular domain of a specificity determining component of an IL-18 receptor; (2) an extracellular domain of a signal transducing component of an IL-18 receptor; and (3) a multimerizing component, wherein the dimer is formed due to the interaction between multimerizing components. Therefore, the above arguments are fully applicable to this rejection and applicants submit that the Examiner has failed to establish a *prima facie* case of anticipation against claim 33 and dependent claims 34-35 because the single fusion protein having two receptor components disclosed by Sims et al. is not capable of dimerizing.

Accordingly, Applicants submit that Sims et al. does not anticipate amended claim 33 or dependent claims 34-35. It is respectfully requested that this rejection be withdrawn.

III. Rejection Under 35 USC § 102(e).

Claims 1-3, 10-19, 25-26, and 29-35 are rejected as anticipated by Sims et al. (US 6,589,764). This rejection is respectfully traversed.

The cited prior art reference. Sims et al. describes multimeric IL-18 receptor polypeptides consisting of IL-1Rrp and AcPL, or fragments thereof. The polypeptides can be co-expressed as dimers formed from fusion proteins IL-1-Rrp:Fc and AcPL:Fc (col. 2, lines 51-56), or one receptor subunit can be fused to the constant region of a immunoglobulin heavy chain and the other receptor

subunit can be fused to the constant region of an immunoglobulin light chain (col. 2, line 56 to col. 3, line 6). Alternatively, the IL-18 receptor may comprise fragments of one receptor complexed with fragments of the other receptor (col. 4, lines 12-20). The two receptor components may be attached through a covalent or non-covalent linkage, e.g., a peptide linker (col. 6, lines 34-58).

In one embodiment disclosed in Sims et al., each receptor is separately linked to an Fc region of an antibody to produce a heterodimer comprising AcPL/Fc linked to IL-1Rrp1/Fc (col. 7, lines 5-23).

The analysis under § 102(e). The above remarks responsive to the rejection under § 102(a) are fully applicable to this rejection and are herein incorporated by reference in their entirety. Applicants respectfully submit that a careful reading of the cited prior art reference shows that Sims et al. does not disclose or suggest a single fusion polypeptide having two receptor components connected to a single Fc component. The above remarks are repeated here only to the extent the supportive citation differs from the WO 99/37772 publication.

The heterodimeric receptor complexes of Sims et al. are of two types: (i) a fusion heterodimeric protein comprising an antibody light chain polypeptide attached to the C-terminus of a soluble first polypeptide or a soluble second polypeptide, and an antibody heavy chain polypeptide attached to the C-terminus of a soluble first polypeptide or a soluble second polypeptide (claim 8) (see also heterodimeric mIL-1Rrp1-Fc/mAcPL-Fc molecules described in Example 4, col. 22, line 35), or (ii) AcPL linked to IL-1Rrp1 (see, for example, col. 18, lines 33-34).

Amended claim 1 requires a nucleic acid molecule to encode a fusion polypeptide that forms a multimer capable of binding IL-18, where the fusion polypeptide has (1) an extracellular domain of a specificity determining component of an IL-18 receptor; (2) an extracellular domain of a signal transducing component of an IL-18 receptor; and (3) a multimerizing component, wherein the multimer is formed due to the interaction between multimerizing components.

Sims et al. discloses a fusion polypeptide which either has (i) component (1) or component (2) and an immunoglobulin domain (3) component, or (ii) component (1) and (2) covalently linked and separated by a peptide linker that functions as a spacer, but not the multimerizing component (3). Embodiment (i) having a first fusion protein having one receptor component and an immunoglobulin can form a dimer with a second fusion protein having the same or a different receptor component, but embodiment (ii) having two receptor components on a single fusion protein cannot form a dimeric protein.

A careful reading of Sims et al. reveals that a peptide linker is not equivalent to multimerizing component. As described at col. 6, line 34 to col. 7, line 4, a peptide linker is employed to separate the two receptor domains by a sufficient distance to ensure that each domain is able to fold into its proper secondary and tertiary structure. The peptide linkers of Sims et al. are placed between the two receptor components and do not function as multimerizing components.

Amended claim 26 differs from claim 1 in that the multimer is limited to a dimer. Therefore, the above arguments are fully applicable to this rejection and applicants submit that the Examiner has failed to establish a *prima facie* case of anticipation against claim 26 and dependent claims 31-32 because the fusion protein disclosed by Sims et al. which has two receptor components is not capable of dimerizing.

Amended claim 33 is drawn to a dimeric IL-18 antagonist comprising two fusion polypeptides, each polypeptide having (1) an extracellular domain of a specificity determining component of an IL-18 receptor; (2) an extracellular domain of a signal transducing component of an IL-18 receptor; and (3) a multimerizing component, wherein the dimer is formed due to the interaction between multimerizing components. Therefore, the above arguments are fully applicable to this rejection and applicants submit that the Examiner has failed to establish a *prima facie* case of anticipation against claim 33 and dependent claims 34-35 because the fusion protein disclosed by Sims et al. that has two receptor components is not capable of dimerizing.

In light of the above remarks, applicants respectfully request that this rejection be withdrawn.

IV. Rejection under § 103(a) is not applicable.

Although the Examiner has not raised an obviousness rejection, applicants herein provide reasoned support for the inapplicability of an obviousness rejected of the instant claims under the cited prior art references.

As discussed above, a careful reading of the cited prior art references disclose two types of fusion proteins disclosed: (i) one in which a fusion protein consists of a single receptor domain connected to an immunoglobulin domain and the two fusion proteins co-expressed in the same cell, or (ii) as a fusion protein in which IL-1Rrp1 is linked to AcPL (WO 99/37772, page 3, lines 5-10). Although both versions are termed "dimeric IL-18 receptor complexes", nowhere is the second version described as containing a multimerizing-type component which would allow such a fusion protein to form a dimer (references to US 6,589,764 are provided in following the WO citation):

Page 3, lines 11-14 (col. 2, lines 51-56) describes cells transfected with DNA encoding IL-1Rrp1:Fc and AcPL:Fc fusion proteins and coexpressed as dimers.

Page 3, lines 15-26 (col. 2, line 57 to col. 3, line 6) describes AcPL/IL-1Rrp1 dimers prepared by fusing one of the receptor subunits to a constant region of an immunoglobulin heavy chain and the other receptor subunit to a constant region of an immunoglobulin light chain.

Page 4, lines 20-38 (col. 3, line 51 to col. 4, line 11) describes dimeric IL-18 receptors that form heteromer complexes in which a soluble AcPl or IL-1Rrp1 fragment is fused to DNA encoding a constant region of a light or heavy chain.

Page 4, line 39 to page 5, line 16 (col. 4, lines 12-32) describes an alternative IL-18 receptor in which one receptor component is non-covalently complexed with the other receptor component. Example of such non-covalent complex formation are given as biotin with avidin.

Page 6, lines 14-16 (col. 5, lines 17-21) describes soluble fusion proteins comprising the extracellular domain of IL-1Rrp1 fused to an antibody Fc region polypeptide and the extracellular domain of AcPL fused to an Fc region polypeptide as described in example 1. Example 1 is an experiment conducted with fusion proteins separately comprising AcPL/Fc and IL-1Rrp1/Fc.

Page 7, line 34 to page 8, line 7 (col. 6, lines 34-50) describes the attachment of an AcPL polypeptide to an IL-1Rrp1 polypeptide through covalent or non-covalent linkages. At page 7, lines 40-41 (col. 6, lines 42-43) it is stated that "Numerous reagents useful for cross-linking one protein molecule to another are known."

Page 8, lines 8-21 (col. 6, line 51 to col. 7, line 4) describes peptide linkers that may be used to separate AcPL and Il-1Rrp1 domains by a distance sufficient to ensure that each domain folds properly.

Page 8, lines 22-23 (col. 7, lines 5-6) describes that AcPL and IL-1Rrp1 are linked via polypeptides derived from immunoglobulins. However, the paragraph goes on to state that a polypeptide derived from an Fc may be attached to the C-terminus of IL-1Rrp1 and a separate Fc polypeptide is attached to the C-terminus of AcPL.

Page 9, lines 9-14 (col. 7, lines 41-48) describes homodimers comprising two IL-1Rrp1/Fc or two AcPL/Fc polypeptides linked via disulfide bonds.

Page 9, lines 15-23 (col. 7, lines 49-61) describes IL-18 receptor complexes including fusion proteins of the constant region of an antibody light chain and the constant region of an antibody heavy chain.

Page 9, line 28 to page 10, line 7 (col. 8, lines 1-23) describes functional heteromeric polypeptides prepared by association between heavy and light chain molecules which normally associate with one another.

Page 10, lines 7-20 (col. 8, lines 24-42) describes fusion proteins in which each receptor domain is individually connected to an immunoglobulin constant region, forming a dimer having two receptor subunits joined by heavy and light chains, or forming a tetramer having four receptor subunits connected through an antibody-like structure, displaying IL-18 binding site bivalently.

This reference at first appears to disclose a structure of the present claims by disclosing a molecule with four IL-18 binding sites. However, in the rejected claims, the grouping of 4 IL-18 binding sites is achieved in a form of a dimer, rather than a tetramer since each fusion protein has two different receptor components.

Sims et al. at page 11, line 25 to page 12, line 26 (col. 9, line 32 to col. 10, line 22) describes constructs which include the C-terminal portion of one receptor subunit fused to a linker which is

fused to the N-terminal portion of the other component. At page 12, lines 21-22 (col. 10, lines 14-16), the specification clearly states that the invention provides DNA sequences encoding fusion proteins comprising AcPL, IL-1Rrp1, and a peptide linker. At page 12, lines 22-24 (col. 10, lines 16-19), the specification goes on to state that DNA encoding AcPL polypeptides disclosed herein are also provided, as is DNA encoding AcPL polypeptides fused to immunoglobulin-derived polypeptides. But the Sims et al. specification fails to mention polypeptides having an immunoglobulin-derived domain which include more than one receptor component.

The above analysis demonstrates that the cited prior art references did not contemplate a single fusion polypeptide having two receptor components and a multimerizing component. In contrast to the invention as presently claimed, the prior art fusion proteins cannot form a dimer having four IL-18 binding sites. Further, there is no suggestion in the cited references that a multimerizing component be attached to a single fusion protein having two receptor subunits. Accordingly, applicants submit that it is only when Sims et al. is read in light of the instant disclosure, that one would combine the elements of the prior art fusion proteins to make the invention as presently claimed.

However, determination of obviousness cannot be based on "the **hindsight** combination of components selectively culled from the prior art to fit the parameters of the patented invention." ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); ATD Corp, 159 F.3d at 546, 48 USPQ2d at 1329; Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.").

Accordingly, applicants submit that the cited prior art references neither disclose or suggest the instant invention.

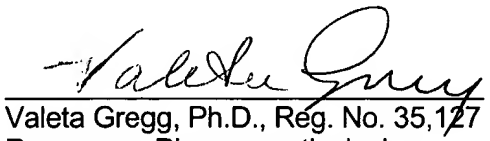
Conclusion

It is believed that this document is fully responsive to the Office action dated 30 Aug 2004. In light of the above amendments and remarks, it is believed that the claims are now in condition for allowance, and such action is respectfully urged.

Fees

This paper is submitted in connection with the above-identified U.S. patent application as a response to the Office Action dated on 30 Aug 2004, which set a three month period for response. Accordingly, this Response is being filed within the three month period and it is believed that no fee is thus due. In the event it is determined that a fee is due, the Commissioner is hereby authorized to charge Deposit Account Number 18-050 in the amount of $110, or any other fees deemed to be due.

Respectfully submitted



Valeta Gregg, Ph.D., Reg. No. 35,127
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, New York 10591
(914) 345-7400

ABSTRACT

The present invention provides a fusion polypeptide capable of binding a cytokine to form a nonfunctional complex. It also provides a nucleic acid sequence encoding the fusion polypeptide and methods of making and uses for the fusion polypeptide.